

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrCUVPOSA™

Glycopyrrolate Oral Solution, 1 mg/5 mL

Anticholinergic

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PrCUVPOSA™
(kuv-POE-suh)
Glycopyrrolate oral solution

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Oral Solution, 1 mg/5 mL	citric acid, glycerin, methylparaben, natural and artificial cherry flavour, propylene glycol, propylparaben, purified water, saccharin sodium, sodium citrate, sorbitol solution

INDICATIONS AND CLINICAL USE

CUVPOSA (glycopyrrolate) is indicated to reduce chronic severe drooling in patients aged 3 –18 years with neurologic conditions associated with problem drooling (e.g., cerebral palsy).

CONTRAINDICATIONS

CUVPOSA is contraindicated in:

- Medical conditions that preclude anticholinergic therapy, for example:
 - Glaucoma
 - Obstructive uropathy, or vesicoureteral reflux
 - Obstructive disease of the gastrointestinal tract
 - Paralytic ileus, or intestinal atony
 - Unstable cardiovascular status
 - Severe ulcerative colitis
 - Toxic megacolon complicating ulcerative colitis
 - Myasthenia gravis
- Patients taking solid oral dosage forms of potassium chloride. The passage of potassium chloride tablets through the gastrointestinal tract may be arrested or delayed with co-administration of CUVPOSA (see **DRUG INTERACTIONS**).
- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

WARNINGS AND PRECAUTIONS

General

Use CUVPOSA with caution in patients with conditions that are exacerbated by anticholinergic drug effects including:

- Autonomic neuropathy
- Renal disease.
- Ulcerative colitis – Large doses may suppress intestinal motility, producing a paralytic ileus and may precipitate or aggravate “toxic megacolon”.
- Hyperthyroidism
- Coronary heart disease, congestive heart failure, cardiac tachyarrhythmias, tachycardia, and hypertension
- Hiatal hernia associated with reflux esophagitis since anticholinergic drugs may aggravate this condition
- Poorly controlled psychiatric conditions, and/or seizures

In the presence of high ambient temperature, heat prostration (fever and heat stroke due to decreased sweating) can occur with the use of anticholinergic drugs such as CUVPOSA. Advise patients/caregivers to avoid exposure of the patient to hot or very warm environmental temperatures.

CUVPOSA may produce drowsiness or blurred vision. As appropriate for a given age, warn the patient not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery, or performing hazardous work while taking CUVPOSA.

Carcinogenesis and mutagenesis: See **TOXICOLOGY**.

Cardiovascular

CUVPOSA is contraindicated in patients with unstable cardiac conditions.

Patients with cardiac arrhythmias, tachycardia, and/or clinically significant ECG abnormalities were excluded from the clinical trials therefore experience in these groups is limited.

Anticholinergic drugs may aggravate or precipitate these conditions. Use CUVPOSA with caution in these patients. Cardiac function and status should be monitored as appropriate, if needed in these patients.

Gastrointestinal

Constipation is a common dose-limiting adverse reaction which sometimes leads to glycopyrrolate discontinuation (see **ADVERSE REACTIONS**). Assess patients for constipation, particularly within 4-5 days of initial dosing or after a dose increase. Intestinal pseudo-obstruction has been reported and may present as abdominal distention, pain, nausea or vomiting.

Diarrhea may be an early symptom of incomplete mechanical intestinal obstruction, especially in

patients with ileostomy or colostomy. If incomplete mechanical intestinal obstruction is suspected, discontinue treatment with CUVPOSA and evaluate for intestinal obstruction.

Renal

Renal Impairment

Because glycopyrrolate is largely renally eliminated, CUVPOSA should be used with caution in patients with renal impairment, and should be avoided in those with severe renal impairment. Systemic exposure to glycopyrrolate can be markedly higher in patients with significant renal impairment as compared to those with normal renal function (see **ACTION AND CLINICAL PHARMACOLOGY, *Special Populations and Conditions*, Renal Insufficiency**).

Urinary Retention

CUVPOSA is contraindicated in patients with urinary retention (e.g., obstructive uropathy). Patients should be instructed to contact a physician immediately if any signs of prostatic hyperplasia or bladder neck obstruction (i.e., difficulty passing urine, painful urination) develop.

Hepatic

Patients with clinically significant hepatic impairment were excluded from the clinical studies. Therefore, the safety and efficacy of CUVPOSA is unknown in children with hepatic disease.

Special Populations

Pregnant Women:

CUVPOSA was not studied in pregnant women. It is also not known whether glycopyrrolate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. In pregnant rats, daily oral administration of glycopyrrolate during organogenesis at doses of 200 and 400 mg/kg/day caused dose-related embryotoxicity. No adverse effects on embryo-fetal development were seen in a study of rabbits dosed intravenously during organogenesis (See **TOXICOLOGY, Reproduction and Teratology**). CUVPOSA should be given to a pregnant woman only if absolutely needed, and the potential benefits of the drug clearly outweigh the possible harm to the embryo / fetus.

Nursing Women: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, CUVPOSA should not be administered to a nursing woman, unless the potential benefits of the drug for the mother clearly outweigh the possible harm to the infant. As with other anticholinergics, glycopyrrolate may cause suppression of lactation.

Pediatrics (<3 years of age): CUVPOSA has not been studied in subjects under the age of 3 years. CUVPOSA is not indicated in children less than 3 years of age.

Geriatrics (≥ 65 years of age): Clinical studies of CUVPOSA did not include subjects aged 65 and over.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The known possible adverse effects of anticholinergics may include: xerostomia; urinary hesitancy/retention; blurred vision (mydriasis and/or cycloplegia); photophobia; increased ocular pressure including acute glaucoma; tachycardia; palpitation; decreased sweating and heat prostration; loss of taste; headache; nervousness; drowsiness; weakness; dizziness; insomnia; nausea; vomiting; impotence; suppression of lactation; constipation; allergic reaction or drug idiosyncrasies including anaphylaxis; some degree of mental confusion and/or excitement.

The most common adverse reactions reported with CUVPOSA are dry mouth, constipation and flushing. Adverse events leading to discontinuation most commonly involved the gastrointestinal system organ class (vomiting and constipation) and psychiatric disorders (abnormal behavior). Dose is titrated based on therapeutic response and adverse reactions.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Study 1: 8-week efficacy/safety

This was a 8-week, double-blind, randomized, placebo-controlled trial to assess the efficacy and safety of CUVPOSA in 38 children with pathologic (chronic moderate to severe) drooling in pediatric patients 3 to 16 years of age with cerebral palsy or other neurologic conditions. Drooling had to be present to the extent that the chin or clothing becomes wet most days. Patients with the following conditions were excluded: glaucoma, obstructive uropathy, vesicoureteral reflux, reactive airway disease, myasthenia gravis, hyperthyroidism, cardiac arrhythmias/tachycardia, or significant ECG abnormalities. Patients were also excluded if they had a history of intestinal obstruction, or had symptomatic gastroesophageal reflux disease, delayed gastric emptying, clinically significant hepatic or renal impairment, had poorly controlled seizures (daily seizures) or had unstable mental disease.

The median age was 10 years, and 58% of patients were males. The underlying condition for 75% of the patients was cerebral palsy. Discontinuation from study due to adverse events was reported in one patient in each group (abdominal distension). Adverse reactions were reported for 75% of patients with CUVPOSA (n=15) and 39% of those with placebo (n=7). The most frequently reported are presented in Table 1.

Table 1 presents adverse reactions reported by > 5% of CUVPOSA-treated subjects and occurring at a greater frequency than placebo in Study 1 (8-week placebo-controlled trial).

Table 1 - Adverse Reactions occurring in >5% of CUVPOSA-treated subjects and at a greater frequency than placebo in Study 1

	CUVPOSA (N=20) n(%)	Placebo (N=18) n(%)
Dry Mouth	8 (40%)	2 (11%)
Vomiting	8 (40%)	2 (11%)
Constipation	7 (35%)	4 (22%)
Flushing	6 (30%)	3 (17%)
Headache	3 (15%)	1 (6%)
Urinary Retention	3 (15%)	0
Heart Rate Increased	2 (10%)	1 (6%)

Adverse reactions occurring in $\leq 5\%$ of CUVPOSA-treated subjects and at a greater frequency than placebo in Study 1 included abdominal distention, agitation, dry lip, dry skin, dyspepsia, excitability, flatulence, irritability, nasal congestion, nasal dryness, and sinusitis.

Study 2: 24-week open label safety study

This was a six-month, multi-center, open-label study to assess the safety of CUVPOSA in 137 children age 3 to 18 years with pathologic (chronic moderate to severe) drooling and cerebral palsy or other neurologic conditions. All patients were to be treated with Cuvposa at dosing regimen comparable to that previously described in Study 1. Patients' selection criteria were also similar to those in Study 1. The average age was 11 years (range: 3 to 18), and 56% of patients were male. A total of 103 (75%) of patients completed the study, and among the 25% who discontinued, 19 patients discontinued the study due to adverse reactions (14%). Approximately 10% of patients experienced a serious adverse event(s); however, causal relationship with CUVPOSA was not clearly established.

The most common adverse reactions were: Constipation, dry mouth, vomiting, flushing, dysuria, diarrhea, epistaxis, urinary retention, lip dry, and urine output decreased.

Less Common Clinical Trial Adverse Drug Reactions (< 2% of patients receiving CUVPOSA) in the 24-week open-label Study 2 are listed below:

Blood and lymphatic system disorders: Anaemia

Gastrointestinal Disorders: Abdominal distention, abdominal pain, chapped lips, retching,

stomach discomfort, tongue dry

General disorders and administration site conditions: Irritability, pain

Infections and infestations: Pneumonia, tracheostomy infection, upper respiratory tract infection, urinary tract infection

Investigations: Alanine aminotransferase increased, bacteria urine, blood albumin decreased, blood bilirubin increased, blood cholesterol increased, oxygen saturation decreased

Metabolism and nutrition disorders: Dehydration

Nervous system disorders: Convulsion, dysgeusia, headache, nystagmus, somnolence

Psychiatric disorders: Abnormal behaviour, aggression, crying, impulse-control disorder, moaning, mood altered, restlessness

Respiratory, thoracic and mediastinal disorders: Increased viscosity of bronchial secretion, nasal congestion, nasal dryness

Skin and subcutaneous tissue disorder: Dry skin, pruritus, rash

Vascular disorder: Pallor

DRUG INTERACTIONS

Drug-Drug Interactions

Drugs Affected by Reduced GI Transit Time

Glycopyrrolate reduces GI transit time, which may result in altered release of certain drugs when formulated in delayed- or controlled-release dosage forms.

- The passage of potassium chloride tablets through the GI tract may be arrested or delayed with coadministration of glycopyrrolate. Solid dosage forms of potassium chloride are contraindicated [see *Contraindications* (4)].
- Digoxin administered as slow dissolution oral tablets may have increased serum levels and enhanced action when administered with glycopyrrolate. Monitor patients receiving slow dissolution digoxin for increased action if glycopyrrolate is coadministered regularly. Consider the use of other oral dosage forms of digoxin (e.g., elixir or capsules).

Drugs Whose Plasma Levels May be Increased by Glycopyrrolate

Coadministration of glycopyrrolate may result in increased levels of certain drugs.

- Atenolol's bioavailability may be increased with coadministration of glycopyrrolate. Monitor patients closely for signs/symptoms of excessive beta-blockade (e.g., reduced heart rate or blood pressure, bronchoconstriction). A reduction in the atenolol dose may be needed.
- Metformin plasma levels may be elevated with coadministration of glycopyrrolate, increasing metformin's pharmacologic and toxic effects. Monitor clinical response to metformin with concomitant glycopyrrolate administration; consider a dose reduction of metformin if warranted.

Drugs Whose Plasma Levels May be Decreased by Glycopyrrolate

Coadministration of glycopyrrolate may result in decreased levels of certain drugs.

- Haloperidol's serum level may be decreased when coadministered with glycopyrrolate, resulting in worsening of schizophrenic symptoms, and development of tardive dyskinesia. Closely monitor patients for signs/symptoms of reduced clinical response to haloperidol when concurrent use cannot be avoided.
- Levodopa's therapeutic effect may be reduced with glycopyrrolate administration. Consider increasing the dose of levodopa.

Drugs that May Enhance the Effect of Glycopyrrolate

- Anticholinergic agents may enhance the anticholinergic effect of glycopyrrolate. Monitor patients closely for excessive anticholinergic effects.
- The anticholinergic effects of glycopyrrolate may be potentiated with concomitant administration of amantadine. Consider decreasing the dose of glycopyrrolate during coadministration of amantadine.
- Monoamine oxidase inhibitors (MAOI) may enhance the orthostatic hypotensive anticholinergic effect of glycopyrrolate. Carefully monitor for orthostatic hypotension with MAOI initiation, or dose increase in patients receiving glycopyrrolate. Gradual MAOI dose increases may help prevent hypotensive effects. A rapid return of blood pressure is often seen upon MAOI dose decrease or discontinuation.

Cannabinoids (dronabinol, nabilone)

Glycopyrrolate may enhance the tachycardic effect of cannabinoids. Monitor cardiovascular status closely.

Drug-Food Interactions

The presence of high fat food reduces the oral bioavailability of CUVPOSA if taken shortly after a meal. Therefore, CUVPOSA should be dosed at least one hour before or two hours after meals (see **DOSAGE AND ADMINISTRATION**).

Drug-Herb Interactions

Interactions with herbal products have not been studied.

Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been studied.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

CUVPOSA must be measured and administered with an accurate measuring device.

Initiate dosing at 0.02 mg/kg orally three times daily and titrate in increments of 0.02 mg/kg

every 5-7 days based on therapeutic response and adverse reactions. The maximum recommended dosage is 0.1 mg/kg three times daily not to exceed 1.5-3 mg per dose based upon weight. For greater detail, see Table 2.

The patient should be weighted regularly (especially younger children), to ensure that the dose received does not exceed the maximum allowed dose indicated in Table 2. Should the bodyweight decrease to a lower weight category, the dosing may have to be adjusted accordingly.

During the four-week titration period, dosing can be increased with the recommended dose titration schedule while ensuring that the anticholinergic adverse events are tolerable. Prior to each increase in dose, review the tolerability of the current dose level with the patient's caregiver.

CUVPOSA should be dosed at least one hour before or two hours after meals.

The presence of high fat food reduces the oral bioavailability of CUVPOSA if taken shortly after a meal (see **CLINICAL PHARMACOLOGY**).

Table 2 - Recommended Dose Titration Schedule (each dose to be given three times daily)

Weight		Dose Level 1		Dose Level 2		Dose Level 3		Dose Level 4		Dose Level 5	
kg	lbs	(~0.02 mg/kg)		(~0.04 mg/kg)		(~0.06 mg/kg)		(~0.08 mg/kg)		(~0.1 mg/kg)	
13-17	27-38	0.3 mg	1.5 mL	0.6 mg	3 mL	0.9 mg	4.5 mL	1.2 mg	6 mL	1.5 mg	7.5 mL
18-22	39-49	0.4 mg	2 mL	0.8 mg	4 mL	1.2 mg	6 mL	1.6 mg	8 mL	2.0 mg	10 mL
23-27	50-60	0.5 mg	2.5 mL	1.0 mg	5 mL	1.5 mg	7.5 mL	2.0 mg	10 mL	2.5 mg	12.5 mL
28-32	61-71	0.6 mg	3 mL	1.2 mg	6 mL	1.8 mg	9 mL	2.4 mg	12 mL	3.0 mg	15 mL
33-37	72-82	0.7 mg	3.5 mL	1.4 mg	7 mL	2.1 mg	10.5 mL	2.8 mg	14 mL	3.0 mg	15 mL
38-42	83-93	0.8 mg	4 mL	1.6 mg	8 mL	2.4 mg	12 mL	3.0 mg	15 mL	3.0 mg	15 mL
43-47	94-104	0.9 mg	4.5 mL	1.8 mg	9 mL	2.7 mg	13.5 mL	3.0 mg	15 mL	3.0 mg	15 mL
≥ 48	≥ 105	1.0 mg	5 mL	2.0 mg	10 mL	3.0 mg	15 mL	3.0 mg	15 mL	3.0 mg	15 mL

Renal impairment

CUVPOSA should be used with caution in patients with renal impairment, and should be avoided in those with severe renal impairment (see ACTION AND CLINICAL PHARMACOLOGY, *Special Populations and Conditions*, Renal Insufficiency).

Missed Dose

If a dose is missed by less than two hours, take the missed dose immediately, unless a meal has been consumed within the past two hours or if a meal will be consumed in the next hour. If a

dose is missed by more than two hours, skip the dose and resume the regular dosing schedule.

OVERDOSAGE

Because glycopyrrolate is a quaternary amine which does not easily cross the blood-brain barrier, symptoms of glycopyrrolate overdose are generally more peripheral in nature rather than central compared to other anticholinergic agents. In case of accidental overdose, therapy may include:

- Maintaining an open airway, providing ventilation as necessary.
- Managing any acute conditions such as hyperthermia, coma and/or seizures as applicable, and managing any jerky myoclonic movements or choreoathetosis, which may lead to rhabdomyolysis in some cases of anticholinergic overdose.
- Administering a quaternary ammonium anticholinesterase such as neostigmine to help alleviate peripheral anticholinergic effects such as anticholinergic induced ileus.
- Administering activated charcoal orally as appropriate.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Glycopyrrolate is a competitive inhibitor of acetylcholine muscarinic receptors that are located on certain peripheral tissues, including salivary glands. Glycopyrrolate indirectly reduces the rate of salivation by preventing the stimulation of these receptors. Because it is a quaternary ammonium compound, glycopyrrolate does not easily cross the blood-brain barrier. Glycopyrrolate effects are thus probably more peripheral than central, compared to other anticholinergic agents.

Pharmacodynamics

Glycopyrrolate inhibits the action of acetylcholine on salivary glands thereby reducing the extent of salivation.

No significant electrocardiogram effects of CUVPOSA were observed in phase 3 studies, except for a clinically relevant increase (10 bpm) in heart rate observed. The data do not suggest that glycopyrrolate would be associated with a clinically marked increase in QTc duration.

Pharmacokinetics

Absorption: In a parallel study of children (n=6 per group) aged 7-14 years undergoing intraocular surgery, subjects received either intravenous (IV) or oral glycopyrrolate as a premedication, the mean absolute bioavailability of oral glycopyrrolate tablets was low (approximately 3%) and highly variable among subjects (range 1.3 to 13.3%). A similar pattern of low and variable relative bioavailability is seen in adults.

Mean C_{max} after oral solution administration in the fasting state was 0.318 ng/mL, and mean AUC_{0-T} was 1.74 ng·hr/mL. Mean time to maximum plasma concentration for CUVPOSA was 3.1 hours, and mean plasma half-life was 3.0 hours.

In healthy adults, a high fat meal was shown to significantly affect the absorption of glycopyrrolate oral solution (10 mL, 1 mg/5 mL). The mean C_{max} under fed high fat meal conditions was approximately 74% lower than the C_{max} observed under fasting conditions. Similarly, mean AUC_{0-T} was reduced by about 78% by the high fat meal compared with the fasting AUC_{0-T} . A high fat meal markedly reduces the oral bioavailability of CUVPOSA. Therefore, CUVPOSA should be dosed at least one hour before or two hours after meals. Pharmacokinetic results (mean \pm SD) are described in Table 3.

Table 3 - Pharmacokinetic Parameters (mean \pm SD) for CUVPOSA, Fasting and Fed, in Healthy Adults treated with a 2 mg single dose (10 mL)

	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-T} (ng·h/mL)	AUC_{0-inf} (ng·h/mL)	$T_{1/2}$ (h)
Fasting (n=37)	0.318 \pm 0.190	3.10 \pm 1.08	1.74 \pm 1.07	1.81 \pm 1.09	3.0 \pm 1.2
Fed (n=36)	0.084 \pm 0.081	2.60 \pm 1.12	0.38 \pm 0.14	0.46 \pm 0.13*	3.2 \pm 1.1*

*n=35

Distribution: After IV administration, glycopyrrolate has a mean volume of distribution in children aged 1 to 14 years of approximately 1.3 to 1.8 L/kg, with a range from 0.7 to 3.9 L/kg. In adults aged 60-75 years, the volume of distribution was lower (0.42 L/kg \pm 0.22).

Metabolism: In adult patients who underwent surgery for cholelithiasis and were given a single IV dose of tritiated glycopyrrolate, approximately 85% of total radioactivity was excreted in urine and <5% was present in T-tube drainage of bile. In both urine and bile, >80% of the radioactivity corresponded to unchanged drug. These data suggest a small proportion of IV glycopyrrolate is excreted as one or more metabolites.

Elimination: Approximately 65-80% of an IV glycopyrrolate dose was eliminated unchanged in urine in adults. In two studies, after IV administration to pediatric patients ages 1-14 years, mean clearance values ranged from 1.01- 1.41 L/kg/hr (range 0.32 -2.22 L/kg/hr). In adults, IV clearance values were 0.54 \pm 0.14 L/kg/hr.

Special Populations and Conditions

Geriatrics: Glycopyrrolate pharmacokinetics have not been characterized in the elderly.

Gender: Population pharmacokinetic evaluation of adults and children administered IV or oral glycopyrrolate identified no effect of gender on glycopyrrolate clearance or systemic exposure.

Race: The pharmacokinetics of glycopyrrolate by race have not been characterized.

Hepatic Insufficiency: Glycopyrrolate is largely renally eliminated. The pharmacokinetics of glycopyrrolate have not been evaluated in patients with hepatic impairment.

Renal Insufficiency: In one study, glycopyrrolate 4 mcg/kg was administered IV in uremic patients undergoing renal transplantation surgery. Mean AUC (10.6 mcg·h/L), mean plasma clearance (0.43 L/hr/kg) and mean 3-hour urinary excretion (0.7%) for glycopyrrolate were significantly different than those of control patients (3.73 mcg·h/L, 1.14 L/hr/kg, and 50%, respectively). These results suggest that elimination of glycopyrrolate is severely impaired in patients with renal failure. CUVPOSA should be used with caution in patients with renal impairment, and should be avoided in those with severe renal impairment (see **WARNINGS AND PRECAUTIONS – Renal**)

STORAGE AND STABILITY

Store at 15° - 25°C. Discard 60 days after opening the bottle.

DOSAGE FORMS, COMPOSITION AND PACKAGING

CUVPOSA is available as 1 mg/5 mL clear, cherry-flavoured solution for oral administration in 473 mL (16 oz) opaque, white high density polyethylene (HDPE) bottles with white polypropylene closures.

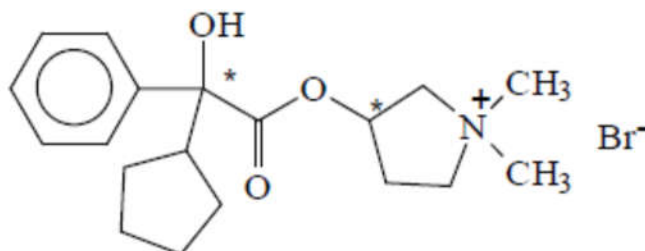
Each mL of oral solution contains 0.2 mg of glycopyrrolate. Nonmedicinal ingredients: citric acid, glycerin, methylparaben, natural and artificial cherry flavour, propylene glycol, propylparaben, purified water, saccharin sodium, sodium citrate, sorbitol solution.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Glycopyrrolate, CAS # 596-51-0 Glycopyrronium bromide, CAS # 51186-83-5
Chemical name:	Pyrrolidinium, 3-[(SR)-(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethyl-, [RS-] bromide (RS)-[3-(SR)-Hydroxy-1,1-dimethylpyrrolidinium bromide] α -cyclopentylmandelate (3RS)-3-[(2SR)-(2-Cyclopentyl-2-hydroxy-2-phenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide
Molecular formula:	C ₁₉ H ₂₈ BrNO ₃
Molecular mass:	398.33
Structural formula:	



Physicochemical properties: Glycopyrrolate is a white, odourless crystalline powder. It is soluble in water and alcohol and practically insoluble in chloroform and ether. Two asymmetric atoms of carbon are present in the molecule of Glycopyrrolate; therefore, four optical isomers exist. Glycopyrrolate produced is represented by the (R,S)-(S,R) pair or *threo* structure.

CLINICAL TRIALS

Study demographics and trial design

Table 4 - Summary of the clinical trial design and patient demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects	Mean age (Range)	Gender
1	Multi-centre, randomized, double-blind, placebo-controlled, parallel group study	CUVPOSA 0.02, 0.04, 0.06, 0.08, 0.1 mg/kg/dose (1 mg/5 mL) or placebo TID; oral; 8 weeks	n = 38	10 (3-23)	22 M; 16 F

F = female; M = male; TID = three times daily

CUVPOSA was evaluated in a multi-center, randomized, double-blind, placebo-controlled, parallel group, eight-week study for the control of pathologic drooling in children. The study enrolled 38 subjects aged 3-23 years; 36 subjects were aged 3-16 years and two patients were older than 16 years. Problem drooling was defined as drooling in the absence of treatment so that clothing became damp on most days (approximately five to seven days per week). Doses of the study medication were titrated over a 4-week period to the optimal response beginning at 0.02 mg/kg three times a day increasing doses in increments of approximately 0.02 mg/kg three times per day every 5-7 days, not to exceed the lesser of approximately 0.1 mg/kg three times per day or 3 mg three times per day.

Subjects were evaluated on the 9-point modified Teacher's Drooling Scale (mTDS), which is presented below.

Modified Teacher's Drooling Scale

1= Dry: never drools

2= Mild: only the lips are wet; occasionally

3= Mild: only the lips are wet; frequently

4= Moderate: wet on lips and chin; occasionally

5= Moderate: wet on the lips and chin; frequently

6= Severe: drools to the extent that clothing becomes damp; occasionally

7= Severe: drools to the extent that clothing becomes damp; frequently

8= Profuse: clothing, hands, tray, and objects became wet; occasionally

9= Profuse: clothing, hands, tray, and objects became wet; frequently

The mTDS evaluations were recorded by parents/caregivers 3 times daily approximately two hours post-dose on evaluation days during pre-treatment baseline and at Weeks 2, 4, 6 and 8 of therapy.

Study results

The underlying condition for 75% of the patients was cerebral palsy. Responders were defined as subjects with at least a 3-point reduction in mean daily mTDS scores from baseline to Week 8.

The proportion of responders in the CUVPOSA treatment group was larger as compared to the placebo group. See Table 5.

Table 5 - Percentage of Responders at Week 8

CUVPOSA Group (N=20)	Placebo Group (N=18)
15/20 (75%)	2/18 (11%)

DETAILED PHARMACOLOGY

Animal Pharmacodynamics

A single IV dose of glycopyrrolate (5 mcg/kg) substantially reduced (by about 50%) methacholine-stimulated salivary secretion in the anesthetized dog. In this study, intravenous (IV) methacholine (11 µg/kg) was given once every 10 minutes for 50 minutes after a single IV injection of glycopyrrolate.

Animal Pharmacokinetics

Pharmacokinetics and metabolism studies were conducted in the mouse, rat, dog and cat using radiolabeled (¹⁴C)-glycopyrrolate. Oral bioavailability of glycopyrrolate was poor, with most radioactivity (80%) excreted in the feces. Only trace amount of glycopyrrolate crossed the blood-brain barrier or placenta, consistent with the quaternary ammonium structure. The main metabolic pathways appear to be hydroxylation and oxidation. With IV or intramuscular administration, excretion of radioactivity was greater in the urine than the feces. Based on the peaks observed in plasma and urinary excretion, there appears to be some enterohepatic recirculation of radioactivity.

Human Pharmacology

See **ACTION AND CLINICAL PHARMACOLOGY**.

TOXICOLOGY

Single-dose Toxicity

Single oral, intra-peritoneal or intravenous administration of glycopyrrolate to mice, rats, rabbits, and dogs was associated with typical muscarinic (anticholinergic) activity comprised of mydriasis, cycloplegia (paralysis of the ciliary muscle), and xerostomia (dry mouth). In rabbits all animals exhibited mydriasis, tachycardia and prostration. At high doses, more significant manifestations encountered were hypoactivity, hypersensitivity, labored respiration, tremors, convulsions, and death.

Table 6 - Acute Toxicity of Glycopyrrolate

Species	Route	LD ₅₀ (mg/kg)
Mouse	Oral	550
	IV	14.7
	IP	107
	IP	112
Rat	Oral	1150
	Oral	1280
	IV	14.6
	IP	196
Rabbits	IV	25
Dogs	IV	15-30

IP = intraperitoneal; IV = intravenous; LD₅₀ = lethal dose 50

Table 7 - Repeat-dose Toxicity

Study type	Species	Route	Dose (mg/kg/day)	Principal findings
14-day	Mouse, CD-1	Oral gavage	0, 30, 60, 120, 250, 500	Severe clinical findings, adverse body weight loss and mortality occurred at 500 mg/kg/day. Test article-related findings in the 250 and 500 mg/kg/day groups included thinness, dermal atonia, decreased defecation and extremities cool to touch. Partial eye closure, consistent with dilated pupils, was noted in the 500 mg/kg/day group males. Yellow and/or brown material was noted on various body surfaces of the 500 mg/kg/day group males and females. Dilated pupils across all treated groups.
13-week	Mouse, CD-1	Oral gavage	0, 30, 100 and 300	Mortality occurred at 100 and 300 mg/kg. Clinical signs in dead/euthanized in extremis animals included impaired equilibrium, intermittent tremors, hypoactivity, prostration, thinness, dermal atonia, body/extremities pale, hypothermia, ptosis, abnormal respiration, swollen abdominal area, soft feces, decreased defecation and/or yellow material on body surfaces. Piloerection in all treated groups. Dilated pupils and lower body weights seen in dose related manner across all treated groups. Histopathology changes in the salivary gland (acinar cell hypertrophy), nasal tissues (degeneration, exudate, inflammation), gingiva (ulceration, inflammation) at ≥ 100 mg/kg/d and Haderian gland (increase in porphyrin pigment) at ≥ 30 mg/kg/d.
14-day	Sprague Dawley Rat	Oral gavage	0, 60, 120, 250, 500, 1000	Mortality occurred at 1000 mg/kg/day. Pupil dilation and lower body weight across all test article groups. Low body weight gains and/or body weight losses, low food consumption, clinical observations of partial eye closure, dermal atonia, body cool to touch, rales, gasping, labored respiration, soft feces, decreased defecation and yellow/brown material on body surfaces in 500 and 1000 mg/kg/day, piloerection at 1000 mg/kg/day.

13-week	Sprague Dawley Rat	Oral gavage	0, 40, 120 and 360	Pupil dilation and lower body weights across all test article groups, red material around eyes slightly increased in 360 mg/kg/day group, rales at 120 and 360 mg/kg/day. Slightly higher mean absolute monocyte counts, higher total urine volume with lower mean specific gravity, osmolality and creatine at 360 mg/kg/day. Histopathology changes including minimal to mild acute inflammation in nasal tissue, larynx, pharynx at 120 and 360 mg/kg/day, mesenteric or mandibular lymph node abscesses at 360 mg/kg/day, mandibular salivary gland (acinar cell hypertrophy) at 120 and 360mg/kg/day, Harderian glands all doses (increased porphyrin pigment) NOAEL=40 mg/kg/day.
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NOAEL= No observed adverse effects level

Carcinogenesis and Mutagenesis

Glycopyrrolate was not carcinogenic in mice up to a dose level of 20 mg/kg/day (the safety margin was 5.1-fold, relative to the maximum recommended human dose [MRHD]), or in rats up to a dose level of 40 mg/kg/day (the safety margin was 21-fold, relative to the MRHD).

In male rats, although there was a notable increase in the incidence of thyroid C-cell adenomas, no linear dose-response trend was noted, and the C-cell adenomas were not locally invasive with no metastases reported. Also, no rats died as a consequence of C-cell tumor in the study. Finally in contrast to humans, the incidence of spontaneous C-cell tumors is known to be high in aging rats. Therefore, glycopyrrolate does not represent a significant carcinogenic risk to humans under the proposed condition of clinical use.

Glycopyrrolate did not elicit any genotoxic effects in the Ames mutagenicity assay, the human lymphocyte chromosome aberration assay, or the micronucleus assay.

Reproduction and Teratology

Glycopyrrolate was assessed for effects on fertility or general reproductive function in rats. Rats of both genders received glycopyrrolate at doses up to 100 mg/kg/day via oral gavage (approximately 50 times the MRHD). No treatment effects on fertility or reproductive parameters of both genders were observed in this study.

Daily oral administration of glycopyrrolate at 50, 200 and 400 mg/kg/day to pregnant rats during organogenesis led to maternal toxicity at all doses, decreased fetal body weights at 200 and 400 mg/kg/day and delays in ossification and embryo-fetal death at 400 mg/kg/day. The No Observed Adverse Effect Level (NOAEL) for developmental toxicity was 50 mg/kg/day (approximately 25 times the MRHD).

In a second study glycopyrrolate administered orally once a day at 50, 200 and 400 mg/kg/day to pregnant rats led to maternal toxicity and significant reduction in body weights of newborns, which persisted though lactation period, and up to approximately 6-11 weeks of postnatal period.

Reduced body weights were noted at all dose levels. The maternal and developmental NOAEL was less than 50 mg/kg/day. Maternal doses of glycopyrrolate as high as 400 mg/kg/day showed no adverse effects on the development of the F1 generation including functional observational battery, memory and learning, and the ability to produce an F2 generation.

In rabbits dosed intravenously during organogenesis up to 1 mg/kg no adverse effects on fetal development were seen even when maternal toxicity was noted. The NOAEL of glycopyrrolate for embryo-fetal development in rabbits is considered to be 1.0 mg/kg/day (approximately 1.1 times the MRHD).

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**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION**

PrCUVPOSA™

(kuv-POE-suh)

glycopyrrolate oral solution

Read this carefully before you start giving **CUVPOSA** to your child and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your child's medical condition and treatment and ask if there is any new information about **CUVPOSA**.

What is CUVPOSA used for?

CUVPOSA is used for reducing drooling caused by certain health problems. It is for patients that are 3-18 years old.

How does CUVPOSA work?

CUVPOSA reduces the rate of drooling. This is done by blocking receptors on the glands that make saliva.

What are the ingredients in CUVPOSA?

Medicinal ingredients: Glycopyrrolate

Non-medicinal ingredients: Citric acid, glycerin, methylparaben, natural and artificial cherry flavour, propylene glycol, propylparaben, purified water, saccharin sodium, sodium citrate, and sorbitol solution.

CUVPOSA comes in the following dosage form:

Oral solution, 1 mg/5 mL.

Do not use CUVPOSA if your child:

- is allergic to glycopyrrolate or any of the other ingredients.
- has an eye problem where the pressure inside the eye is too high (glaucoma).
- has a blockage or backward flow of urine drainage from the kidney, ureter, or bladder.
- has a blockage that keeps food or liquid from passing through the small or large intestine.
- has a blockage in the intestine due to either paralysis or weakening of the intestinal muscles.
- has unstable cardiovascular status.
- has severe ulcerative colitis with or without other serious bowel problems.
- has a disease that makes the voluntary muscles more weak and tired.
- is taking a solid oral form (e.g. a tablet) of potassium chloride.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you give your child CUVPOSA. Talk about any health conditions or problems you may have, including if your child:

- has any stomach or bowel problems, including ulcerative colitis.
- has any problems with constipation.
- has any problems with diarrhea.
- has thyroid problems.
- has high blood pressure.
- has heart problems or abnormal heart beats.
- has a hiatal hernia with gastroesophageal reflux disease (GERD).
- has any problems urinating.
- has any other medical conditions.
- is pregnant or plans to become pregnant. It is not known if CUVPOSA can harm an unborn baby.
- is breastfeeding or plans to breastfeed. It is not known if CUVPOSA passes into breast milk and if it can harm the baby.
- has kidney problems.
- has poorly controlled mental conditions and/or seizures.

Other warnings you should know about:

CUVPOSA can cause your child to sweat less. Your child can become overheated. If your child is in an area that is very hot, they may develop heat stroke.

CUVPOSA may cause sleepiness or blurred vision. Your child should not drive a car or operate heavy machinery. Your child should not do other risky activities while taking CUVPOSA.

Tell your healthcare professional about all the medicines your child takes, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with CUVPOSA:

- anticholinergic agents (diphenhydramine, phenothiazines, tricyclic antidepressants)
- amantadine
- atenolol
- cannabinoids (dronabinol, nabilone)
- digoxin
- haloperidol
- levodopa
- metformin
- monoamine oxidase inhibitors (e.g. moclobemide, phenelzine, procarbazine, rasagiline, selegiline, tranylcypromine)
- solid oral dosage forms of potassium chloride

Ask your healthcare provider or pharmacist if you are not sure if a medicine your child takes is one that is listed above.

How to give CUVPOSA:

- Give 1 hour before or 2 hours after meals.
- Give exactly as prescribed by your child's doctor. Do not change the dose of CUVPOSA unless your doctor tells you to.
- Pour the approximate dose into a specially marked dose measuring cup, then use an oral syringe to accurately measure the correct amount of CUVPOSA. Dosing cups and oral syringes are available at most pharmacies. **DO NOT insert the oral syringes into the bottle.**
- For questions on how to measure the dose or use an oral syringe, ask your pharmacist or doctor.
- Administer the dose using the oral syringe. Make sure that your child swallows the dose.
- **Thoroughly wash the syringe and dose cup with warm water after each use.**
- **Any unused solution remaining in the dose cup should be discarded after each use.**
- **The syringe and dose cup should be clean and dry prior to each use.**
- Discard 60 days after opening the bottle.

Usual dose:

Your doctor will tell you how much CUVPOSA (millilitres or mLs) to give your child. The usual starting dose is 0.02 mg/kg orally three times daily. Your doctor will adjust the dose over time based on your child's response and side effects. The maximum recommended dose is 0.1 mg/kg three times daily and should not be greater than 1.5 – 3 mg (7.5 mL – 15 mL) per dose based upon weight.

Overdose:

If you think you have given your child too much CUVPOSA, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss giving a dose of CUVPOSA to your child and it is:

- within 2 hours of the usual dose time, give your child the missed dose immediately, unless a meal has been eaten within the last 2 hours. Do not feed your child a meal for 1 hour after giving them CUVPOSA.
- more than 2 hours since the usual dose time, do not give your child the missed dose. Give the next dose at the regular dose time.

Do not give your child a double dose to make up for a forgotten dose.

What are possible side effects from using CUVPOSA?

These are not all the possible side effects you may feel when taking CUVPOSA. If you experience any side effects not listed here, contact your healthcare professional. Please also see **Other warnings you should know about.**

The most common side effects of CUVPOSA include:

- dry mouth.
- vomiting.
- constipation.
- flushing of the face or skin.
- headache.
- problem urinating, difficulty starting urination.
- rapid heart beat.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<p>VERY COMMON Constipation:</p> <ul style="list-style-type: none"> • Straining with bowel movements. • Longer time between bowel movements. • Cannot have a bowel movement. • Stomach is firm and large. 		X	
<p>COMMON Diarrhea:</p> <ul style="list-style-type: none"> • This can be an early symptom of intestinal blockage. This is more likely if your child has had a colostomy or ileostomy. 		X	
<p>UNKNOWN Problems with control of body temperature:</p> <ul style="list-style-type: none"> • Hot and red skin. • Less alert or passing out. • Fast and weak pulse. • Fast and shallow breathing. • Fever. 		X	

If your child has a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your child's daily activities, talk to your healthcare professional.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at [MedEffect](#);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 1908C
Ottawa, ON
K1A 0K9Postage paid labels and the Consumer Side Effect Reporting Form are available at [MedEffect](#).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at 15°C - 25°C.

Keep CUVPOSA out of reach and sight of children.

If you want more information about CUVPOSA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](#); the manufacturer's website www.medexus.com or by calling 1-877-630-5674.

This leaflet was prepared by Medexus Pharmaceuticals Inc.

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